

Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents

Results From a Registry of 18,334 Patients

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Objectives This study sought to compare the risk of stent thrombosis among patients treated with bare-metal stents (BMS), first-generation drug-eluting stents (G1-DES), and second-generation drug-eluting stents (G2-DES) for a period of 3 years.

Background In patients undergoing coronary stenting, there is a scarcity of long-term follow-up data on cohorts large enough to compare rates of stent thrombosis across the stent generations.

Methods A total of 18,334 patients undergoing successful coronary stent implantation from 1998 to 2011 at 2 centers in Munich, Germany, were included in this study. Patients were stratified into 3 groups according to treatment with BMS, G1-DES, and G2-DES.

Results The cumulative incidence of definite stent thrombosis at 3 years was 1.5% with BMS, 2.2% with G1-DES, and 1.0% with G2-DES. On multivariate analysis, G1-DES compared with BMS showed a significantly higher risk of stent thrombosis (odds ratio [OR]: 2.05; 95% confidence interval [CI]: 1.47 to 2.86; $p < 0.001$). G2-DES were associated with a similar risk of stent thrombosis compared with BMS (OR: 0.82; 95% CI: 0.56 to 1.19; $p = 0.30$). Beyond 1 year, the risk of stent thrombosis was significantly increased with G1-DES compared with BMS (OR: 4.72; 95% CI: 2.01 to 11.1; $p < 0.001$), but not with G2-DES compared with BMS (OR: 1.01; 95% CI: 0.32 to 3.25; $p = 0.98$).

Conclusions In a large cohort of unselected patients undergoing coronary stenting, compared with BMS, there was a significant excess risk of stent thrombosis at 3 years with G1-DES, driven by an increased risk of stent thrombosis events beyond 1 year. G2-DES were associated with a similar risk of stent thrombosis compared with BMS. (J Am Coll Cardiol Intv 2013;6:1267–74) © 2013 by the American College of Cardiology Foundation

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Stent thrombosis is a rare but frequently fatal complication of percutaneous coronary intervention (1,2). First-generation drug-eluting stents (G1-DES), compared with bare-metal stents (BMS), markedly reduce the need for reinterventions (3-6). However, the risk to be borne appears to be a small but continuous increase in the incidence of stent thrombosis in the late phase after stent implantation (7-9). Pathological samples of patients with stent thrombosis confirmed that G1-DES lead to delayed arterial healing, incomplete endothelialization, and persistent fibrin deposition compared with BMS (10). The use of durable polymer coatings, the thickness of the stent struts, and the dose of the antiproliferative drug and its release kinetics have been implicated as important contributing factors in these late adverse events (11-13). Against this background, second-generation DES (G2-DES) were developed that have improved biocompatibility, durable or biodegradable polymer coatings, thinner stent struts, and improved antiproliferative drug release kinetics. Indeed G2-DES have

shown favorable safety and efficacy compared with G1-DES in a number of clinical trials and registries (14-18). To date, however, there is a scarcity of long-term follow-up data on real-world patients in cohorts large enough to compare rates of stent thrombosis with adequate statistical power across different generations of stents. The aim of this study was to compare the relative risk of stent thrombosis among 3 different stent generations, BMS, G1-DES, and G2-

Abbreviations and Acronyms

BMS = bare-metal stent(s)

CI = confidence interval

DES = drug-eluting stent(s)

G1-DES = first-generation drug-eluting stent(s)

G2-DES = second-generation drug-eluting stent(s)

OR = odds ratio

STEMI = ST-segment elevation myocardial infarction

DES, from a dataset of 18,334 patients with coronary artery disease treated with intracoronary stents over a 13-year period.

Methods

Patient selection and study procedures. We analyzed clinical, angiographic, and procedural data for all consecutive patients treated with stent implantation for coronary artery disease between January 1998 and December 2011 in 2 tertiary referral centers in Munich, Germany (Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum Rechts der Isar) provided that written informed consent was obtained. Patients receiving long-term renal replacement therapy and those who had undergone previous cardiac transplantation or with stent thrombosis as an indication for intervention were excluded. BMS were the sole platforms approved for use from January 1998 to August 2002. Thereafter, DES became available. DES were arbitrarily subclassified as first or second generation. G1-DES

comprised durable polymer (polyethylene-co-vinyl acetate and poly-*N*-butyl-methacrylate sirolimus-eluting stents (Cypher, Cordis, Warren, New Jersey); durable polymer (Translute) paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts), durable polymer (phosphorylcholine) zotarolimus-eluting stents (Endeavor, Medtronic Inc., Santa Rosa, California), and polymer-free sirolimus-eluting stents (Yukon, Translumina GmbH, Hechingen, Germany); the majority of G1-DES were Cypher and Taxus stents. G2-DES were available starting in January 2006 and comprised durable fluoropolymer everolimus-eluting stents (Xience V, Abbott Vascular, Santa Clara, California), durable polymer (BioLinX) zotarolimus-eluting stents (Resolute, Medtronic Inc.), biodegradable polymer biolimus A9-eluting stents (Nobori, Terumo Corporation, Tokyo, Japan), biodegradable polymer sirolimus-eluting stents and polymer-free sirolimus and probucol-eluting stents (both Yukon; Translumina GmbH); the majority of 2G-DES were Xience and Resolute stents. The assignment to BMS or DES platforms occurred predominantly in the setting of randomized trials; typically, the same stent was implanted in a patient undergoing multilesion interventions. Antithrombotic and anticoagulant therapies reflected the changing practices during the period of observation. Until April 1999, in patients undergoing a percutaneous coronary intervention, we used the ticlopidine therapy regimen, which comprised a pre-treatment dose of 500 mg given orally 1 to several hours before the procedure followed by a 500-mg/day maintenance dose. From May to August 1999, patients received clopidogrel therapy consisting of pre-treatment with an oral dose of 300 mg given 2 to 4 h before the intervention, 150 mg/day until discharge, and a maintenance dose of 75 mg/day. Since September 1999, we initiated a high loading clopidogrel regimen with an oral dose of 600 mg of clopidogrel, 150 mg/day until discharge, and a maintenance dose of 75 mg/day. After the intervention, all patients, irrespective of treatment allocation, were prescribed 200 mg/day of aspirin indefinitely, whereas ticlopidine or clopidogrel was prescribed for a period of at least 1 month after BMS implantation and at least 6 months after DES implantation. During coronary intervention, all patients received anticoagulation with either unfractionated heparin or bivalirudin. Administration of glycoprotein IIb/IIIa inhibitors and the use of intracoronary imaging was at the discretion of the operating physician. After the intervention, patients remained in the hospital for at least 48 h. Blood samples were drawn every 8 h for the first 24 h after randomization and daily afterward for the determination of cardiac markers (creatinine kinase, creatine kinase-myocardial band, troponin T or I). Daily electrocardiography was also performed until discharge. All patients were prescribed standard secondary prevention for coronary artery disease as directed by the treating physician (e.g., beta-blockers, statins, angiotensin-converting enzyme inhibitors, and other

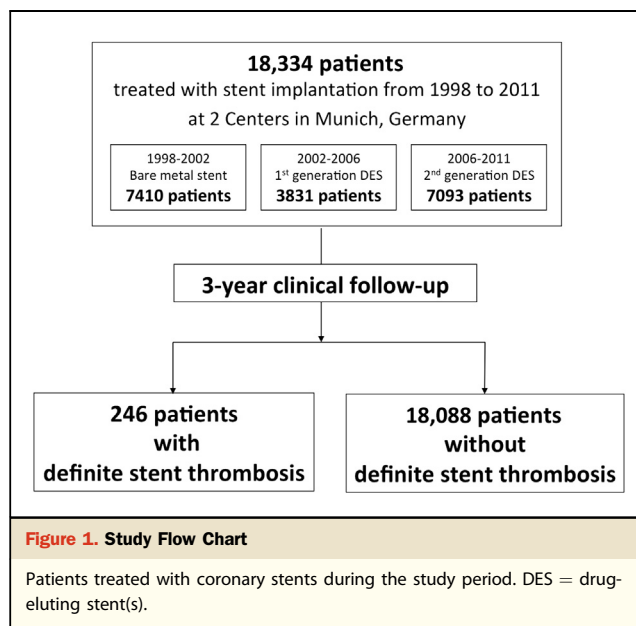
drugs). All patients were then evaluated at 1, 12, and 36 months by phone or office visit.

Data management, endpoints, and definitions. Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Center. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups. Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed offline in the quantitative angiographic core laboratory (ISAResearch Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands) by independent experienced operators unaware of the treatment allocation. Measurements were performed on cine angiograms recorded after the intracoronary administration of nitroglycerin using the same single worst-view projection at all times. The contrast-filled nontapered catheter tip was used for calibration. Quantitative analysis was performed on both the in-stent and in-segment area (including the stented segment as well as both 5-mm margins proximal and distal to the stent). Qualitative morphological lesion characteristics were characterized by standard criteria.

The primary endpoint was the 3-year Academic Research Consortium definite stent thrombosis confirmed by angiography or autopsy (19). The secondary endpoint was very late definite stent thrombosis occurring beyond 1 year. Successful stent implantation was achieved if residual stenosis after intervention was <30% with Thrombolysis In Myocardial Infarction flow grade 3. Risk factors and comorbidities in each patient were determined as recorded by the treating physician. Acute coronary syndrome was defined as acute myocardial ischemia on the basis of clinical symptoms, electrocardiography changes, and increase in cardiac biomarkers and comprised acute ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina.

Statistical analysis. Categorical data are presented as count and percentage. Continuous data are presented as median and interquartile range (25th, 75th percentiles) or mean \pm SD, as appropriate. Data distribution was tested for normality using the Kolmogorov-Smirnov test. For patient level data, the differences among groups were checked for significance using the Student *t* or Kruskal-Wallis test (continuous data) or the chi-square test. For lesion-level data, differences among groups were checked for statistical significance using generalized estimating equations for non-normally distributed data to address intrapatient correlation in patients who underwent multilesion interventions (20).

The incidence of stent thrombosis was calculated at lesion level. For 3-year overall stent thrombosis, cumulative incidence was estimated with the Kaplan-Meier method, and differences among groups were tested with the log-rank test. For very late stent thrombosis beyond 1 year, incidence



rates were calculated relative to the number of patient-years under observation (expressed as the number of events/1,000 patient-years). In contrast to crude percentages, incidence rates take into account differences in the follow-up duration among stent generations. A multivariate regression analysis was performed to assess predictors of stent thrombosis. All clinical, angiographic, and procedural features reporting a *p* value <0.05 on univariate analysis were included in the model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were used as summary statistics and were derived from generalized estimating equation models. The statistical software package R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for analyses. The R package gee was used to perform multivariate analyses (21).

Results

Overall 3-year incidence of definite stent thrombosis. The 18,334 patients with 28,739 lesions enrolled in this study were treated as follows: 7,410 patients (40.4%) received BMS in 10,708 lesions; 3,831 patients (20.9%) received G1-DES in 5,872 lesions; and 7,093 patients (38.7%) received G2-DES in 12,159 lesions (Fig. 1). Baseline clinical characteristics and lesion and procedural characteristics among BMS, G1-DES, and G2-DES are shown in Online Tables 1 and 2.

At 3 years, definite stent thrombosis had occurred in 246 patients (1.3%) with 292 lesions. All the stent thromboses were confirmed by angiography. Baseline clinical characteristics differed significantly between those with and without stent thrombosis at 3 years (Table 1). In addition,

Table 1. Baseline Clinical Characteristics

	Stent Thrombosis	No Stent Thrombosis	p Value
No. of patients	246	18,088	
Age, yrs	65.9 ± 12.0	66.9 ± 11.4	0.25
Female	57 (23.2)	4,678 (25.9)	0.39
Body mass index, kg/m ²	27.0 ± 4.4	27.2 ± 4.3	0.55
Diabetes mellitus	96 (39.0)	4,664 (25.8)	<0.001
Insulin-treated	35 (14.2)	1,466 (8.1)	0.001
Hypertension	132 (53.7)	11,609 (64.2)	0.001
Hyperlipidemia	153 (62.2)	10,986 (60.7)	0.69
Current smoker	67 (27.2)	3,794 (21.0)	0.02
Previous MI	100 (40.7)	4,326 (23.9)	<0.001
Previous bypass surgery	28 (11.4)	2,102 (11.6)	>0.99
Multivessel disease	210 (85.4)	13,634 (75.4)	<0.001
Cardiogenic shock at presentation	17 (6.9)	811 (4.5)	0.09
ST-segment elevation MI	70 (28.5)	3,846 (21.3)	0.008
Acute coronary syndrome	134 (54.5)	8,611 (47.6)	0.03
Left ventricular ejection fraction	48.9 ± 13.6	52.8 ± 13.2	<0.001

Values are n, mean ± SD, or n (%).
MI = myocardial infarction.

angiographic and procedural characteristics were also significantly different (Table 2). In short, greater cardiac comorbidity, acute presentations and complex comorbidities as well as higher lesion complexity were more likely to be present in the stent thrombosis group.

At 3 years, definite stent thrombosis was found in 118 lesions (1.5%) in BMS, 92 lesions (2.2%) in G1-DES, and 82 lesions (1.0%) in G2-DES (Fig. 2). Only 4 patients with stent thrombosis had different stent types in the same vessel tract where the stent thrombosis was located.

On multivariate analysis adjusted for covariates, compared with BMS, the adjusted odds ratio for definite stent thrombosis was 2.05 (95% CI: 1.47 to 2.86; $p < 0.001$) in G1-DES and 0.82 (95% CI: 0.56 to 1.19; $p = 0.30$) in G2-DES. Figure 3 shows the complete set of variables included in the multivariate analysis. Diabetes mellitus, current smoker, history of prior myocardial infarction, clinical presentation with STEMI, complex lesion morphology, in-stent restenosis, and a 5% increase in residual stenosis were independent predictive factors for stent thrombosis.

Incidence of definite stent thrombosis at 30 days. At 30 days, definite stent thrombosis occurred in 72 lesions (0.7%) in BMS, in 44 lesions (0.7%) in G1-DES, and in 57 lesions (0.5%) in G2-DES. After adjustment for inpatient correlation and differences in baseline characteristics, there were no significant differences among 3 stent generations (adjusted rates of stent thrombosis: 0.6% in BMS, 0.7% in G1-DES, and 0.5% in G2-DES, $p = 0.074$).

Definite stent thrombosis between 1 and 3 years. Landmark analysis was conducted for assessing the risk of very late definite stent thrombosis across the groups between 1 and

Table 2. Lesion and Procedural Characteristics

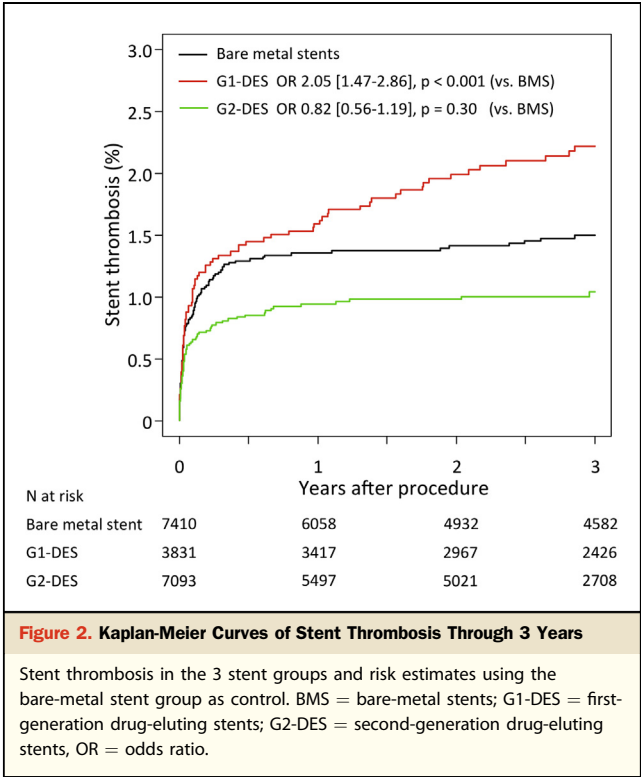
	Stent Thrombosis	No Stent Thrombosis	p Value*
No. of lesions	292	28,447	
Lesion location			<0.001
Left anterior descending coronary artery	145 (49.7)	12,195 (42.9)	
Left circumflex coronary artery	53 (18.2)	6,421 (22.6)	
Right coronary artery	70 (24.0)	7,941 (27.9)	
Left main trunk	8 (2.7)	1,187 (4.2)	
Saphenous vein graft	16 (5.5)	696 (2.4)	
Complex lesion (B2/C)	250 (85.6)	22,312 (78.4)	0.002
Chronic total occlusion	12 (4.1)	1,358 (4.8)	0.48
In-stent restenosis	44 (4.6)	909 (3.2)	<0.001
Stent type			<0.001
Bare-metal stent	118 (40.4)	10,590 (37.2)	
Drug-eluting stent	174 (59.6)	17,857 (62.8)	
First-generation drug-eluting stent	92 (31.5)	5,780 (20.3)	
Second-generation drug-eluting stent	82 (28.1)	12,077 (42.5)	
Total stented length, mm	27.3 ± 15.2	24.8 ± 15.2	0.001
QCA parameters			
Lesion length, mm	16.2 ± 10.9	15.2 ± 9.1	0.06
Vessel size, mm	2.81 ± 0.55	2.88 ± 0.57	0.03
Minimum lumen diameter, mm			
Before procedure	0.83 ± 0.56	0.92 ± 0.56	0.03
Post procedure	2.52 ± 0.60	2.70 ± 0.55	<0.001
Stenosis, %			
Before procedure	69.8 ± 19.6	68.1 ± 17.9	0.22
Post procedure	13.1 ± 13.5	10.0 ± 9.3	<0.001
Maximal balloon diameter, mm	3.12 ± 0.59	3.21 ± 0.57	0.007
Balloon-to-vessel ratio	1.12 ± 0.11	1.12 ± 0.12	0.88
Maximal balloon pressure, mm	14.1 ± 3.13	14.5 ± 3.10	0.01

Values are n (%) or mean ± SD. *p value was calculated with generalized estimating equation models to adjust clustering data.
QCA = quantitative coronary angiography.

3 years. The rate of definite very late stent thrombosis was 0.5/1,000 patient-years in BMS, 3.3/1,000 patient-years in G1-DES, and 0.4/1,000 patient-years in G2-DES (Fig. 4). On multivariate analysis, the risk of very late stent thrombosis was significantly increased with G1-DES compared with BMS (adjusted OR: 4.72; 95% CI: 2.01 to 11.1; $p < 0.001$). In contrast, the risk of very late stent thrombosis was similar between G2-DES and BMS (adjusted OR: 1.01; 95% CI: 0.32 to 3.25; $p = 0.98$). Stent implantation for in-stent restenosis and saphenous vein grafts were independently associated with increased risk of very late stent thrombosis (Fig. 5).

Discussion

In the present study, we compared the relative risk of stent thrombosis among 3 different intracoronary stent



generations in 18,334 patients undergoing percutaneous intervention at 2 centers in Munich, Germany, over a period of 13 years. The main findings are: 1) percutaneous coronary

intervention with G1-DES compared with BMS had a significantly greater risk of definite stent thrombosis at 3 years; 2) intervention with G2-DES compared with BMS was associated with a statistically similar risk of stent thrombosis through 3 years; 3) the presence of diabetes mellitus, current cigarette smoking, history of myocardial infarction, STEMI at presentation, complex lesion morphology, in-stent restenosis, and increased residual stenosis after stenting independently predicted overall 3-year stent thrombosis; and 4) beyond 1 year, the use of G1-DES but not G2-DES predicted the risk of stent thrombosis.

Because concerns regarding the long-term safety of DES such as late and very late stent thrombosis are thought to be more apparent when DES were implanted for so-called off-label use (22), the large patient cohort with unrestricted use of intracoronary stents in our study strengthens the generalizability of the results to real-world practice of percutaneous coronary interventions. The current study confirms the excess risk of stent thrombosis observed with G1-DES compared with BMS. Moreover, there is strong evidence to suggest that this risk has been eliminated with the use of G2-DES. These findings are in line with observations from recent studies reporting the improved safety of G2-DES compared with G1-DES (14–18). Indeed, our data showed a numerically lower incidence of stent thrombosis with G2-DES compared with BMS, especially in the early phase of follow-up. Although this difference was not statistically significant, it is consistent with observations by Palmerini et al. (15) from an indirect comparison network

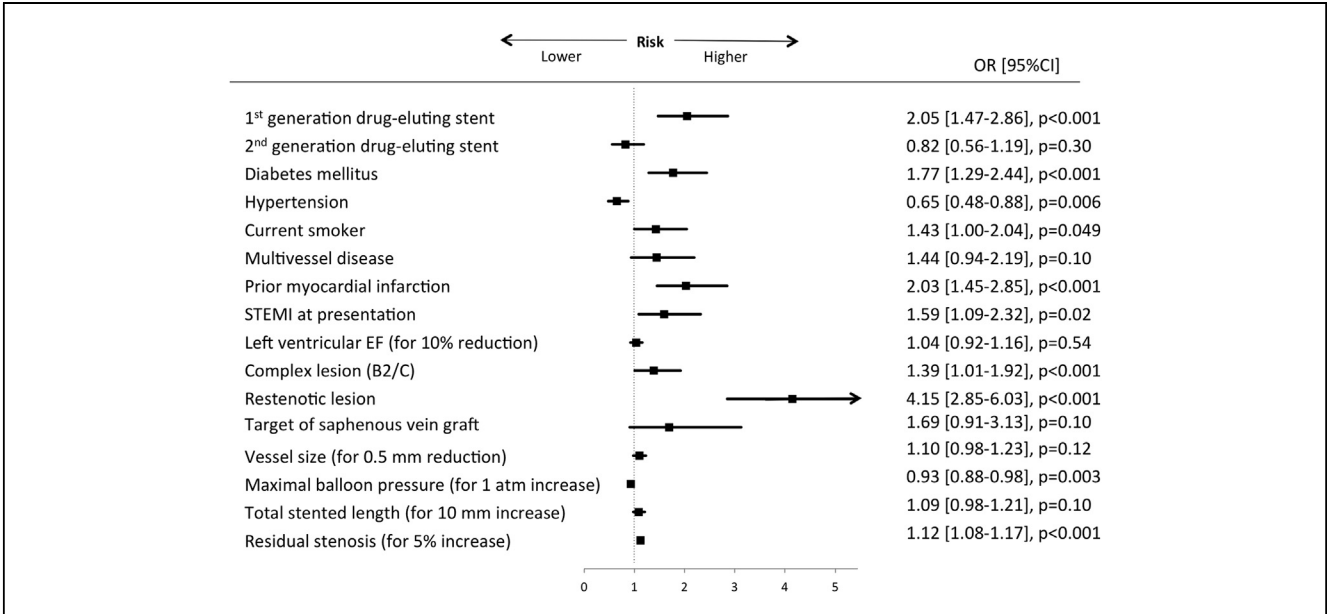


Figure 3. Risk Estimates of Predictors of Stent Thrombosis Through 3 Years

Plots of the OR for variables associated with a higher or lower risk of stent thrombosis. The center indicates the point estimate and the left and the right sides of the line the 95% confidence interval. CI = confidence interval; EF = ejection fraction, OR = odds ratio; STEMI = ST-segment elevation myocardial infarction.

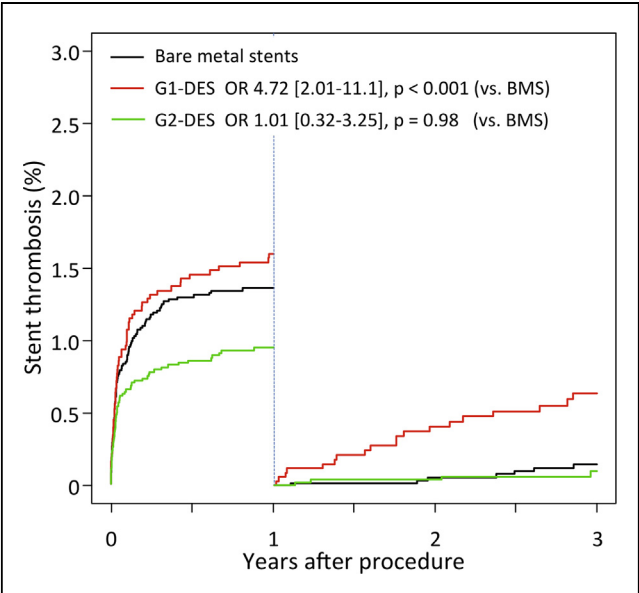


Figure 4. Landmark Analysis of Stent Thrombosis

Stent thrombosis is shown for the first year and for the period after the first year, separately. Abbreviations as in Figure 2.

meta-analysis suggesting a lower risk of stent thrombosis in patients with everolimus-eluting stents compared with both non-everolimus DES and BMS. Patients enrolled in the present study reflect everyday practice with minimal exclusion criteria.

The reason for the lower risk of stent thrombosis observed with G2-DES remain unclear. Pathophysiological mechanisms underlying improved safety with G2-DES compared with their predecessors remain speculative, although newer stent technologies such as more biocompatible and/or biodegradable polymers, improved drug-eluting kinetics, thinner strut platforms, and their combination may contribute to long-term lower thrombogenicity after implantation (23–27). Indeed, pathological and intracoronary imaging studies showed evidence of improved arterial healing including higher neointimal coverage and fewer intrastent thrombi after G2-DES implantation compared with G1-DES (28,29).

An additional consequence of delayed arterial healing after coronary stenting is accelerated in-stent neoatherosclerosis. Rupture of these plaques inside the implanted stent may be another important trigger for late and very late stent thrombosis (30). The more rapid time course of neoatherosclerotic change with G1-DES compared with BMS (31–33) may explain the increased risk of very late stent thrombosis with G1-DES. A post-mortem histological study reported that the earliest atherosclerotic change began at 4 months after sirolimus-eluting stent implantation, whereas the same change in BMS lesions first occurred beyond 2 years (32).

Regarding potential mechanisms to explain the low incidence of stent thrombosis events in the early phase of follow-up after G2-DES implantation where re-endothelialization of stent struts is expected to be incomplete (34), biocompatible polymer coatings such as fluoropolymer in the

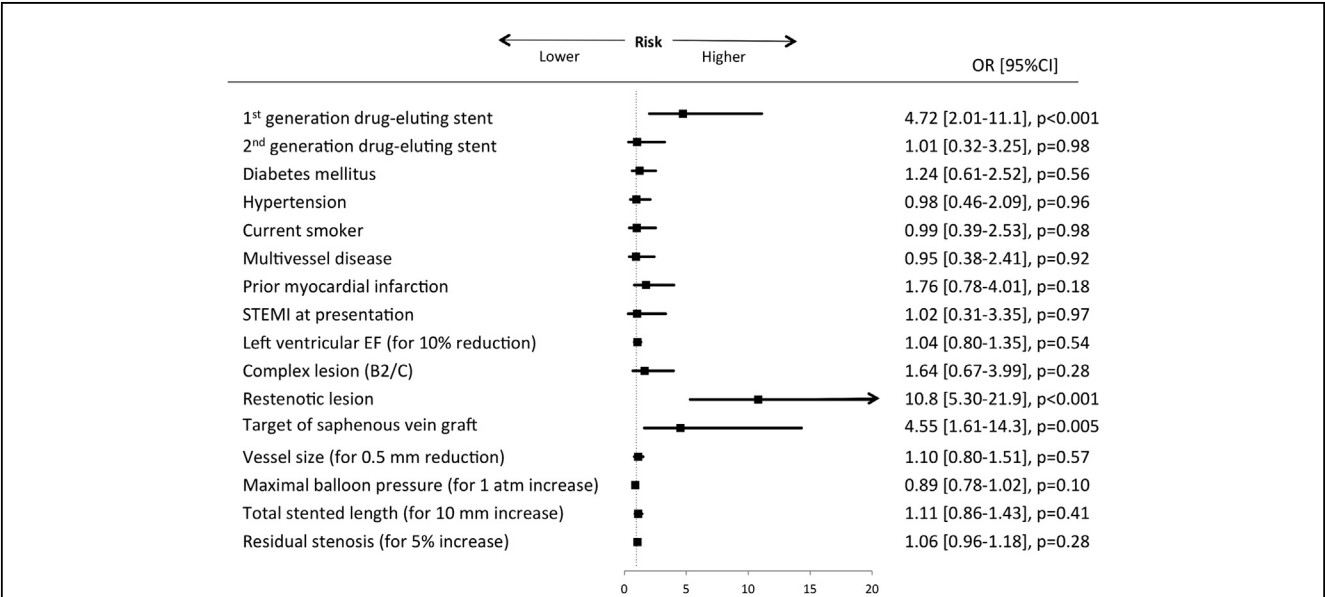


Figure 5. Risk Estimates of Predictors of Very Late Stent Thrombosis

Plot of OR for variables associated with higher or lower risk of stent thrombosis. The center indicates the point estimate and the left and the right ends of the line the 95% confidence interval. Abbreviations as in Figure 3.

everolimus-eluting stent (23,27), BioLinx polymer in the Resolute zotarolimus-eluting stent (35), and polylactic acid biodegradable polymers (16,26) may act protectively against thrombogenicity of the foreign bodies in the implanted segment.

Consistent with previous studies (36,37), we found that patient comorbidities and lesion complexity were associated with the overall incidence of definite stent thrombosis at 3 years. In addition, it is noteworthy that restenting for in-stent restenosis was the strongest predictive factor for both overall and very late stent thrombosis. Using DES for in-stent restenosis has been supported by evidence reporting its superior efficacy in preventing recurrence of restenosis compared with both plain balloon angioplasty (38,39) and vascular brachytherapy (40,41). However, these studies were not designed and powered to evaluate long-term safety of this treatment strategy. Emerging technologies using time-limited systems for drug delivery to the diseased vessel such as drug-eluting balloon or drug-eluting biodegradable scaffolds may be a promising alternative (42–44).

After a series of studies reporting increased death or myocardial infarction after DES implantation in mid-2006 (45–47), increasing concern for late stent thrombosis resulted in an abrupt decline in the use of DES (48). The present study supports the improved long-term safety of the interventions with the G2-DES over its predecessors and, at the same time, suggests that timely and accurate reporting of outcomes after the introduction of new technologies allows better understanding of potential problems and facilitates evolution of these devices.

Study limitations. First, this study lacks a randomized design, and stent selection was based only on the period-specific availability of the devices. As such, findings in relation to the comparative safety of different stent generations should be interpreted with caution and are hypothesis generating in nature. However, analyses were adjusted for confounders using multivariate analysis with generalized estimation equation models, thus minimizing the potential for bias. Second, we did not include duration of or compliance with medications in this study because it is difficult to reliably ascertain data concerning the prevalence of medication adherence or the timing of antiplatelet therapy discontinuation in such a large-scale registry. Third, this study included only cases adjudicated as Academic Research Consortium–definite stent thrombosis (i.e., confirmed by angiography or autopsy). Although this may have resulted in an underestimation of the true prevalence of stent thrombosis, each individual event could be clearly attributed to a single stent analyzed at the lesion level. Moreover, although use of a lesion-level analysis is important to permit capture of lesion-specific factors relevant to stent thrombosis, to minimize potential bias introduced by inpatient correlation, an inherent issue in lesion-specific analysis, comparisons across the groups were adjusted using generalized estimation

equation models. Fourth, the ability of multivariate analysis to fully adjust for the considerable differences in baseline characteristics as well as the improvement in interventional and periprocedural treatment strategies over time might be questionable. More frequent post-dilation, thrombus aspiration, and the use of new antithrombotic medications may have contributed to an improved outcome among patients with G2-DES compared with patients with BMS and G1-DES. Finally, grouping of stents as BMS, G1-DES, and G2-DES is necessarily arbitrary and cannot fully capture differences across different BMS or DES platforms.

Conclusions

In a large cohort of unselected patients undergoing coronary stenting compared with BMS, there was a significantly increased risk of stent thrombosis at 3 years with G1-DES driven by an excess of stent thrombosis beyond 1 year. G2-DES were associated with similar risk of stent thrombosis compared with BMS.

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Key Words: bare-metal stent(s) ■ drug-eluting stent(s) ■ stent thrombosis.

APPENDIX

For supplemental material, please see the online version of this article.